HOPE FOR THE FUTURE:
DEVELOPING AN HIV/AIDS VACCINE

Hearing before the

Committee on Foreign Relations
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Honorable Richard Lugar, Chairman

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Prepared Statement By

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Let me express my thanks to the Chair and this committee for holding this hearing to learn more about progress in HIV vaccine research. It is an honor to appear before you and with Dr. Anthony Fauci of the National Institutes of Health (NIH) and Dr. Seth Berkley of the International AIDS Vaccine Initiative (IAVI). Thank you also to Ashley Judd for your very informative remarks.

I am Dr. Helene Gayle and serve as the director of HIV, Tuberculosis, and Reproductive Health at the Bill & Melinda Gates Foundation. I am also co-chair of the Global HIV Vaccine Enterprise, serving with Dr. Michel Kazatchkine, who is France's Ambassador on HIV/AIDS and Transmissible Diseases. In addition, I serve as president of the International AIDS Society and co-chair of the Global HIV Prevention Working Group.

In my testimony today, I will discuss the importance of an HIV vaccine in the fight against AIDS, the work of our foundation in supporting HIV vaccine research, the establishment of the Global HIV Vaccine Enterprise, and finally a few thoughts on the role of an HIV vaccine within the broader picture of HIV prevention and treatment.

Last year, more people were infected with HIV than in any previous year. The nearly 5 million children, women, and men who were newly infected in 2004 brought the total number of people living with HIV worldwide to nearly 40 million. A few weeks ago, the Centers for Disease Control and Prevention (CDC) announced that here in the United

States the number of people living with HIV topped 1 million. You are all aware of the human and financial cost that lies behind these numbers so I won't elaborate further, other than to say that the epidemic continues to outpace our efforts to contain it, and the road ahead is indeed long. More, much more, must be done now if we are to have a chance of beating this deadly virus.

Ultimately, a safe and effective preventive vaccine offers the best long-term hope for stopping the spread of HIV. Put another way, there is no conceivable way to end this epidemic without a vaccine. Thus, global efforts in the vaccine field must be seen as of the highest priority, but should not have to compete with the equally important need to expand current HIV prevention and treatment services, or with other aspects of our efforts to fight poverty and eradicate disease.

Much good research has been done, and important progress has been made toward a vaccine. Scientists across the globe have been working on finding a vaccine for about as long as we have known about HIV. The United States has been a leader in the global search for a vaccine, largely through the efforts of NIH, and also through the Army Medical Research program, the CDC, and countless laboratories in academic research institutions and pharmaceutical and biotechnology companies throughout the country. Our nation leads the world in biomedical research capacity, and so we have led the world in HIV vaccine research.

These efforts have taught us a great deal about the virus: how it enters the body, establishes itself, multiplies, and evades and undermines the immune system. Though far from a cure, drugs have been developed that can, for many, substantially slow the impact of the virus. These antiretrovirals – ARVs – give hope to millions who are living with HIV infection.

Yet despite all of this tremendous work, progress in finding an HIV vaccine has been too slow. If we measure the end of the pipeline for vaccine candidates, we see only a few drips. While a number of candidate vaccines have been tested in human trials over the last 18 years, only one approach has completed the Phase III trials that ultimately are needed to establish whether something that worked in a test tube is effective in humans. Sadly, no candidate vaccine has yet emerged with demonstrated capacity to prevent HIV infection. Additional research progress is urgently needed to develop a new generation of candidate vaccines with a better chance of success than those currently being evaluated.

All of us are disappointed that we currently lack a safe and effective preventive vaccine. Those of us who are participating in this hearing are united in our desire to make the search for an HIV vaccine as short as possible. An understanding of the history of vaccine research, though, helps us put into proper context the global effort that is currently underway. This year we commemorate the 50th anniversary of the vaccine against polio – the one developed by Jonas Salk. Few people remember that it took many years for Dr. Salk and his colleagues to travel from concept to an approved product. Indeed, the first two trials for the Salk vaccine occurred in the mid 1930s. Moreover, the

vaccine that was successfully tested 50 years ago was subsequently improved by additional research.

In the case of HIV, certain basic scientific questions remain unanswered, and critical areas of research merit substantially greater attention. In 2003, the Bill & Melinda Gates Foundation joined with a group of international researchers and vaccine experts, including Dr. Fauci from the NIH and other U.S. government officials, and Dr. Berkley from IAVI, to author an article in *Science* magazine that described these challenges in more detail and proposed a new global effort to address them. (I have attached a copy of this article and ask that it be incorporated into the record.) We called for creation of a global alliance, modeled in many ways on the Human Genome Project, to concentrate and accelerate the world's HIV vaccine research efforts.

This was the start of the Global HIV Vaccine Enterprise, which is an alliance of researchers, advocates, donor agencies, and others united in their commitment to work together to accelerate HIV vaccine research. Soon thereafter, six working groups were established, bringing together some of the best scientists and advocates, to design a blueprint for action. Early this year, the results of their work were presented with the publication of the Enterprise's Scientific Strategic Plan. It identified six areas for concentrated work and collaboration:

> Vaccine Discovery: While vaccines for some other diseases have succeeded by triggering an antibody response, there is now a strong consensus that an effective vaccine for HIV will need both to generate a broad-based antibody response that can neutralize the virus and recruit and influence the immune cells that suppress the virus's ability to replicate and evade the immune system.
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> The Strategic Plan proposes a two-pronged approach to broaden the candidate pipeline. First, we should expedite rigorous testing and comparative evaluation of candidates currently in the pipeline, although none of these is believed to induce the full range of immune responses that scientists believe will be required. Second, new and better candidates must be developed to widen the product pipeline. Simply put, we must speed up clinical research on what we have, and push more vaccine candidates into the pipeline.
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> Laboratory standardization: Improving collaboration and strategic prioritization in the vaccine field requires that we have a common way of understanding trial results and comparing different candidates. We need to build tools and systems that enable scientists working across the globe to compare their work from one laboratory to another, and from one clinical trial to another.
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> Product development and manufacturing: Processes will be needed for producing consistent, active vaccine batches on a sufficient scale to meet the needs of large clinical trials and eventually worldwide demand. Typically, manufacturing processes are built slowly over time, as each vaccine candidate advances from early clinical testing to late-stage evaluation and licensure. Worldwide capacity

for manufacturing new products is limited and exists almost exclusively in the private sector, which usually gears its capacity in the early years of a product to address demand in high-income countries.

The historic reliance on private industry for manufacturing capacity may not meet the world's needs in the case of an HIV vaccine. Few private companies are presently engaged in any form of vaccine research, and many fewer still are involved in HIV vaccine research. To address the manufacturing needs associated with vaccine research, the number of private sector organizations working on HIV vaccines should significantly increase, and product development and manufacturing capacity should be built in the non-profit and governmental sectors.

Building clinical trial capacity: Demonstrating that a candidate vaccine works in humans is difficult, time consuming, and expensive. Global capacity to conduct this research is limited, especially the large Phase III studies that involve tens of thousands of healthy human volunteers. Research on vaccines and other new prevention technologies is best conducted in parts of the world where HIV is hitting hardest because this is where we most urgently need to know if a vaccine is safe and effective. Yet these areas are already reeling from the effects of the epidemic, and as we have seen in the struggle to expand access to current prevention and treatment services, there are simply not enough trained people and adequate facilities to do this work at an accelerated pace.

Building regulatory capacity: In this country, we all benefit from the oversight provided by the Food and Drug Administration, which helps ensure that medical products on the market are safe and effective. This capacity does not exist or is very weak in many of the countries hit hardest by AIDS, so their ability to regulate HIV vaccine clinical research and to ensure that clinical research is conducted safely and ethically is quite limited. Weak national regulatory structures can significantly delay the initiation of clinical trials and the approval of new products.

Intellectual property issues: Intellectual property issues often inhibit the flow of information and dialogue among researchers. To permit and encourage the active, real-time collaboration needed to accelerate HIV vaccine research, a framework is needed that allows organizations working on novel vaccine candidates to share information openly without compromising protection of their intellectual property.

(I have attached a copy of the full Strategic Scientific Plan and ask that it be incorporated into the record.)

Having identified these six core focus areas, the Enterprise aims to create new groups and mechanisms to the monitor the Plan and to make appropriate revisions as necessary.

The Enterprise is not a new institution that will make grants or conduct biomedical research on its own, and the Enterprise's Scientific Strategic Plan is not intended to describe the entirety of HIV vaccine research. Rather, the Enterprise is an alliance for strategic planning, collaboration and information-sharing, and its Plan focuses on the key challenges that will most benefit from global collaboration. The Enterprise is premised on the belief that finding a preventive HIV vaccine could be accelerated by an approach that augments the traditional paradigm for biomedical research. The usual research approach relies principally on individual research teams, working independently from others, generating incremental progress. This way of doing business is still important but by itself may not be sufficiently targeted to most efficiently reach the goal of an effective HIV vaccine.

To have a meaningful impact on the global search for a vaccine, the Scientific Strategic Plan must be shared with, and embraced by, others that have important roles to play. We hope that funders of HIV vaccine research will use the Plan to guide their allocation of new resources – both to direct resources toward key challenges and to ensure that recipients of such funds adhere to the spirit of collaboration and transparency represented by the Enterprise. This doesn't mean that we want to stifle innovation. Just the opposite. We strongly believe that greater communication and collaboration are essential to speeding up our progress. One example of support for the priorities identified in the Enterprise Strategic Plan is the resources that NIH will make available for a new Center for HIV/AIDS Vaccine Immunology.

In October, the Enterprise will convene a Funders Forum, hosted by the Wellcome Trust in London, to bring together those currently funding HIV vaccine research with those that could potentially provide additional resources. The Funders Forum will help current and future donors better understand the Enterprise and its Scientific Strategic Plan, and our hope is that it will also persuade them to use the Plan as a guiding tool in their funding processes. We are also hopeful that other donor countries and private foundations and businesses will soon be in a position to commit new resources towards the Enterprise plan.

The Enterprise also intends to engage policy makers, advocates, clinical trial hosts and volunteers, regulatory and host government officials, and others. The first meeting of stakeholders was held in May of this year, also in London, and was co-hosted by the Enterprise and the United Kingdom's Department for International Development (DfID). We are also working to establish a permanent secretariat for the Enterprise and have launched an international search for its first executive director.

The U.S. government has played a very important role in the birth and development of the Enterprise. At last year's Sea Island summit of G8 nations, the U.S. shepherded through a strong statement of political support for the Enterprise and announced the first financial contribution to implement the Enterprise's strategic vision. (I have attached a copy of the G8's endorsement to this statement and ask that it be incorporated into the record.)

I was also very pleased that the goals of the Enterprise were highlighted in an op-ed in January, 2005 in *The Washington Post* by Chairman Lugar and by Patty Stonesifer, President and Co-chair of the Gates Foundation. (The op-ed is attached, and I ask that it be incorporated into the record.)

Let me now briefly describe the work of our foundation in supporting HIV vaccine research. It is a critical part of our broader global health agenda, which focuses on a fundamental commitment by Bill and Melinda Gates to global health equity. It is both a philosophical premise that people shouldn't suffer from illness and disease simply because they were born into poverty, and an understanding that improving health is fundamental to fighting poverty and giving every child an equal chance at a safe and productive life.

Our commitment to HIV vaccine research has been longstanding, initially reflected through our support for the International AIDS Vaccine Initiative, to which we have made grants totaling $126.5 million. IAVI, which is based in New York City, is a not-for-profit organization that conducts HIV vaccine research through partnerships with private industry and developing world scientists and also advocates for a greater global response in this area. IAVI is a partner in developing the HIV Vaccine Enterprise. We also support the work of the AIDS Vaccine Advocacy Coalition, also based in New York and an Enterprise partner, which is a small organization with a big, informed voice that helps to monitor global progress on HIV vaccine research.

More recently, we have helped to launch the Enterprise and are currently serving as its interim secretariat. The foundation announced in February a commitment of up to $360 million over five years to fund work on scientific priorities identified by the Enterprise Plan, including development of novel candidate vaccines and laboratory standardization. I should tell you that the response was overwhelming. We received more than $1.4 billion in requests for support, many of which were for serious, innovative research. We are now in the process of identifying those that best match the goals of our request for proposals, but there clearly is great, unmet demand by researchers.

We are also committed to doing more over time. We work closely with our colleagues at the NIH, the Wellcome Trust, and other government and research agencies across the world to leverage our resources with those from others. We hope that more resources are forthcoming, because a significant gap exists between resources currently available for vaccine research and amounts needed to finance a robust research effort. IAVI has estimated that $700 million was spent worldwide on HIV vaccine research last year, including in the public and private sectors, and that as much as $1.2 billion per year may be needed to develop a more robust and comprehensive approach. That gap of $500 million is about equal to what the NIH is currently investing in this area, so we need others to step up to the plate.

Finally, let me describe how HIV vaccines fit into the broader context of the global effort on HIV/AIDS. Vaccines are part of the long-term strategy to prevent expansion of the epidemic. In all probability, we will not have a safe, effective preventive HIV vaccine

for more than a decade. I would be delighted were my projection to prove too pessimistic, but this timeframe represents the best estimate among leaders in the field. Moreover, developing the kind of preventive vaccine that can halt the epidemic will likely happen in stages, with the first generation of vaccines protecting only some people some of the time, and then improving over time to protect more people all of the time. Because an estimated 95% of all new HIV infections occur in developing countries, we would also hope to see vaccines that require one shot instead of three, that would not need refrigeration, and that could be easily administered. This will take time.

Even a very good vaccine will not be a silver bullet. It will take time to get the vaccine to those at risk. We see even today that vaccines that are cheap and effective sit on shelves while millions of children suffer and die needlessly. Our track record for getting vaccines to those who need them is poor. Even after a safe and effective vaccine emerges, we will also need to continue and possibly even expand our other prevention efforts.

For the medium term, we see the importance of developing other new tools to expand options for slowing the spread of HIV. We know that our current strategies aimed at abstinence, faithfulness, condom use, treatment of other sexually transmitted disease, and encouraging people to be tested for HIV can make a difference if they reach the people who need these the most. HIV infection remains 100% preventable, but today fewer than one in five adults at high risk for HIV have access to existing prevention information or services. We also know that existing methods of prevention don't serve the needs of all populations and all life circumstances. This is especially true for women, who now represent roughly one-half of all new HIV infections worldwide and about 30% of new infections in this country. Many women are at risk for HIV not because of their own behaviors but because of the behavior of their male partners. It is critical to invest in research on microbicides, vaginal ointments or gels, female barriers like diaphragms or female condoms, and use of anti-HIV medications for prevention – these are all potential methods for women to protect themselves from HIV without requiring their partner's knowledge or permission. These will be our best hope for reducing the spread of HIV in the short to medium term.

Providing life-preserving therapies, such as antiretroviral drugs, is a pressing global priority. At the current rate, however, another 50-60 million people will have contracted HIV during the 10 years it might take to find an HIV vaccine. Unless the rate of new infections is sharply reduced through prevention, demand for antiretrovirals will rapidly outstrip the world's financial and technical means to deliver them. Effective prevention helps preserve the promise of HIV treatment.

Let me conclude by suggesting what you can do to help:

1. More funding is needed. We know that this is a familiar refrain, and the American people have been extremely generous in the global fight against AIDS. We need to continue to expand our efforts and to do so at a faster pace. We will find an HIV vaccine to help bring an end to this global nightmare, and that day will come

much sooner if researchers have the funding to do their work.

I mentioned earlier that the G8 endorsed the Enterprise at its summit last year. In two weeks, G8 leaders will gather again in the United Kingdom. We hope that the upcoming summit meeting will generate a reaffirmation of the G8's commitment to the Enterprise, and we would appreciate any assistance that members of this committee could provide in encouraging the Administration to advocate for continued G8 support for a robust global vaccine research effort.

2. We need to engage the private sector. There is a wealth of talent and knowledge and experience in the private sector that we must have to be successful, although too few companies have joined this effort. The reasons aren't complicated: vaccine research is risky, expensive, and the financial payouts are small in comparison to more lucrative pharmaceuticals. Moreover, we don't yet have enough candidate vaccines with demonstrated efficacy in the test tube to excite private sector investments. You can help by supporting the purchase and use of vaccines that are currently available – there's no better inducement to private investment than knowing that there's a market ready, willing, and able to purchase their products. If they see the vaccines we have now gathering dust on the shelf, why should they believe that an HIV vaccine will be treated any differently?

   We also need to increase support for programs that provide incentives for private companies to conduct global health research. With incentives, industry is a willing partner. A good example is BIO Ventures for Global Health (BVGH), an initiative of the biotechnology industry and charitable foundations to overcome the market barriers, funding barriers, and information barriers that have long restricted biotech firms from conducting research into diseases that primarily affect developing countries. BVGH is working with companies and foundations to build new partnerships and is preparing a series of business cases that describe market and funding opportunities for biotech firms to increase their involvement in global health research. In addition, BVGH has represented the biotech industry in negotiations with finance ministers over the role that advance purchase agreements can play in spurring research into critical solutions like HIV and malaria vaccines.

3. We need to support a comprehensive approach to HIV. All that you are doing now to support the expansion of prevention and treatment services for HIV is extremely helpful in our HIV vaccine research work. As an example, in the course of clinical research on vaccine candidates, thousands of volunteers are screened and tested. For this research to be ethical, they need to be provided access to the best prevention and treatment services available regardless of whether they are enrolled in the trial. If the responsibility for providing these prevention and treatment services falls onto the research project itself, the financial burden is so substantial that the research itself is inhibited. On the other hand, if other programs like the Global Fund to Fight AIDS, Tuberculosis, and

Malaria or the President's Emergency Plan for AIDS Relief (PEPFAR) are able to step in to fund those services, the research can move forward without carrying the load for an entire community.

4. We need your patience. This will be a long, tough road, and there will be more failures than successes. That is the nature of scientific research, and we need to know that you will persevere with political commitment and resources until we've accomplished our goal.

I thank all of you, and particularly Chairman Lugar, for your interest in this area, your commitment to U.S. leadership in the fight against this terrible epidemic, and your special interest in supporting the global effort to find a safe and effective preventive HIV vaccine.

Let me also acknowledge the tremendous leader we all have in Dr. Fauci. He has been a stalwart supporter of the Global HIV Vaccine Enterprise, and a real partner to our foundation in this and so many other areas of biomedical research.

Thank you again for allowing me to share my thoughts with you. I look forward to your questions.

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ATTACHMENTS

1. "Speeding an AIDS Vaccine." Opinion piece by Senator Richard Lugar and Patty Stonesifer.

2. "G-8 Action to Endorse and Establish a Global HIV Vaccine Enterprise."

3. "The Need for a Global HIV Vaccine Enterprise." Richard D. Klausner, Anthony S. Fauci, Lawrence Corey, Gary J. Nabel, Helene Gayle, Seth Berkley, Barton F. Haynes, David Baltimore, Chris Collins, R. Gordon Douglas, Jose Esparza, Donald P. Francis, N. K. Ganguly, Julie Louise Gerberding, Margaret I. Johnston, Michel D. Kazatchkine, Andrew J. McMichael, Malegapuru W. Makgoba, Giuseppe Pantaleo, Peter Piot, Yiming Shao, Edmund Tramont, Harold Varmus, Judith N. Wasserheit. *Science*, Vol 300, Issue 5628, 2036-2039 , 27 June 2003

4. "The Global HIV/AIDS Vaccine Enterprise: Scientific Strategic Plan." Coordinating Committee of the Global HIV/AIDS Vaccine Enterprise. *PLoS Med* 2(2): e25.

Speeding an AIDS Vaccine
By Richard G. Lugar and Patty Stonesifer

Washington Post
Wednesday, January 19, 2005; Page A19

Picture two scientists in adjacent labs. They're working on the same problem -- how to stop a disease that kills 3 million people every year -- but although they compare notes and share findings, they need a better plan to coordinate their research. They labor for years at the same task, but as individuals rather than as a community of scientists. Although they make important progress, after two decades just one vaccine makes it into large-scale clinical trials -- and it doesn't work.

With a few exceptions, this has been the story of the search for an HIV vaccine. While dedicated scientists around the world have collaborated on significant discoveries, they've had no shared strategy for finding a preventive vaccine, no standardized tools to compare results, no forum to identify priorities and share information. Meanwhile, HIV-AIDS is spreading at an alarming pace, with a record 4.8 million new infections in 2003. At the current rate, there will be 45 million new infections by 2010 and nearly 70 million more deaths by 2020.

Preventing the transmission of HIV-AIDS by discovering and making accessible an effective vaccine must be a priority for our government, for the private sector and academia, and for other countries, including the Group of Eight industrial nations. While promising results are coming from new approaches to changing behavior, such as the Ugandan "ABC" model -- which promotes abstinence, being faithful and condoms -- that is clearly not enough.

Fortunately, a group of the world's leading scientists is mobilizing to coordinate and improve vaccine efforts. This alliance of independent organizations, called the Global HIV Vaccine Enterprise, is committed to accelerating the development of a preventive HIV vaccine by working more collaboratively, more strategically and more aggressively.

But such a risky and expensive venture can succeed only if government leaders, donors and researchers around the world work together to make it happen. And while the progress so far has been promising, there's much more to do. This year will present three concrete opportunities to achieve real progress for the Global HIV Vaccine Enterprise.

First, Congress must continue to make the fight against AIDS a priority in U.S. foreign policy and in future spending. Besides causing massive human suffering and loss of life, the disease is undermining the stability of nations, creating labor shortages and making orphans of an entire generation of children. President Bush, through his Emergency Plan for AIDS Relief, has provided new leadership and resources for the worldwide campaign to fight the disease. The federal government, through the National Institutes of Health, already has one Vaccine Research Center and, in support of the Global HIV Vaccine

Enterprise, has unveiled plans for a second one. The NIH's continued leadership and support are critical.

Congress, businesses, foundations and others must fund the Global HIV Vaccine Enterprise and its components, including vaccine research centers. The investment we make now in finding a vaccine will not only save millions of lives but could save billions of dollars in future treatment costs. We also need to determine whether tax or other incentives will be necessary to get the most talented private-sector scientists to contribute to this enterprise, and whether we need to help developing countries improve their pharmaceutical regulations to break down barriers that discourage collaboration.

Second, governments, scientists, donors, the private sector and community leaders must act on a set of priorities to help accelerate the search for a vaccine. The Global HIV Vaccine Enterprise brought many of the world's leading researchers together to develop just such a blueprint, which for the first time identifies key research priorities. The blueprint, which was published yesterday, calls for new approaches to crack the major scientific barriers to an HIV vaccine, for affected countries to host more clinical trials and train more researchers, for more private-sector investment in research and development, and for local leaders to encourage volunteers to participate in studies. It is a global summons to action.

Finally, other developed countries must make this project a priority by focusing their resources on it. The G-8 industrial nations endorsed the Global HIV Vaccine Enterprise at their 2004 summit, and AIDS-ravaged Africa will be at the top of their agenda when they meet in July in Scotland. Now is the moment for these countries -- Japan, Germany, France, Britain, Canada, Italy and Russia -- to make real commitments to support the enterprise, for instance by creating their own vaccine research centers and linking them in a global effort.

This year we can make genuine headway in the fight against AIDS -- a pandemic that threatens mankind in a way no other disease has. In the 1960s we launched the Apollo program to put a man on the moon. In the 1990s we came together to map the human genome. In the decade ahead why shouldn't we demand a similarly urgent effort -- this time an international one -- to stop this scourge?

Richard G. Lugar is a Republican senator from Indiana and chairman of the Senate Foreign Relations Committee. Patty Stonesifer is co-chair and president of the Bill & Melinda Gates Foundation.

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G-8 ACTION TO ENDORSE AND ESTABLISH A GLOBAL HIV VACCINE ENTERPRISE

1. We reaffirm our commitment to combating the global HIV/AIDS pandemic. Both individually and collectively, we have increased our efforts aimed at HIV treatment, care, and prevention. We acknowledge the important role of the Global Fund to Fight AIDS, Tuberculosis, and Malaria, UNAIDS, and WHO in fighting this pandemic. But the human and economic toll of the AIDS pandemic demands that these activities be complemented by accelerated efforts to develop an HIV vaccine. In 2001 and 2002, only seven vaccine candidates entered clinical trials, and only one entered advanced human testing, but proved to be ineffective. Vaccine development efforts have proceeded slowly, due largely to the enormous scientific challenges. The best way to meet these challenges is for scientists around the world to work together in a complementary manner.

2. We believe the time is right for the major scientific and other stakeholders -- both public and private sector, in developed and developing countries -- to come together in a more organized fashion. This concept has been proposed by an international group of scientists. Published as a "Policy Forum" in Science magazine. Klausner, RD, Fauci AS, et al: "The need for a global HIV vaccine enterprise." Science 300:2036, 2003. We endorse this concept and call for the establishment of a Global HIV Vaccine Enterprise – a virtual consortium to accelerate HIV vaccine development by enhancing coordination, information sharing, and collaboration globally.

3. The Enterprise should establish a strategic plan that would prioritize the scientific challenges to be addressed, coordinate research and product development efforts, and encourage greater use of information sharing networks and technologies. This plan should serve as a blueprint for helping to align better existing resources and to channel more efficiently to the needs at hand new resources as they become available. Specifically, the strategic plan should seek to:

3.1. Encourage the development of a number of coordinated global HIV Vaccine Development Centers: Each center should have the critical mass and scientific expertise to advance the development of a particular HIV vaccine approach. These centers could be self-contained, as is the National Institute of Allergy and Infectious Diseases (NIAID) Vaccine Research Center at the U.S. National Institutes of Health, the European Research Institutes or could be virtual centers, such as those funded by the public-private partnerships of the International AIDS Vaccine Initiative (IAVI), the European Developing Countries Clinical Trials Program (EDCTP), the Gates Foundation, and others.

3.2. Stimulate the development of increased dedicated HIV vaccine manufacturing capacity: There is inadequate existing capacity to produce HIV vaccines for advanced clinical testing. Therefore, the resources and facilities involved in manufacturing potential HIV vaccines must be increased, particularly for testing of vaccine candidates that are currently in or will soon be in the developmental pipeline, like in the EDCTP.

3.3. Establish standardized preclinical and clinical laboratory assessment: Data gathered from clinical trials on a given vaccine candidate should be available and applicable to trials being conducted on other vaccine candidates. Therefore, standardized protocols and measures of effectiveness need to be adopted at the preclinical and clinical stages of vaccine development. In turn, laboratories need to be better linked to clinical trials, which will require wider use of novel confidentiality agreements and information-sharing technologies.

3.4. Expand an integrated international clinical trials system: Large, clinical programs capable of conducting phase I, II, and III trials of potential HIV vaccines have been established by the U.S. NIAID, France 's Agence Nationale de Recherches sur le SIDA, Italy 's National AIDS Program, IAVI, and the EU. This global clinical trials system should be expanded and coordinated. It should facilitate a multidisciplinary approach which draws in inputs from social and behavioral scientists, alongside biomedical teams.

3.5. Optimize interactions among regulatory authorities: Increased cooperation, communication and sharing of information among regulatory authorities in various countries and regions involved in licensing HIV vaccines are essential. This can be accomplished without reducing safety or manufacturing standards.

3.6. Encourage greater engagement by scientists from developing countries: Since most phase III trials will need to be conducted in the developing countries hardest hit by the disease, the international clinical trials system must involve local scientists, ethical review committees comprised of local and international representatives, and regulatory bodies.

4. We call on all stakeholders in the Global HIV Vaccine Enterprise to complete the development of this strategic plan by our next Summit.

5. The United States, in its role as president of the G-8, will convene later this year a meeting of all interested stakeholders in the Enterprise to encourage their collaborative efforts in HIV vaccine development. This meeting should clarify how the strategic plan is to be implemented. We support this conference becoming an annual event and we look forward to a report on the follow-up of the Initiative at the next G-8 Summit.

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From the U.S. State Department web site at:
http://usinfo.state.gov/ei/Archive/2004/Jun/10-92350.html

POLICY FORUM

MEDICINE

The Need for a Global HIV Vaccine Enterprise

Richard D. Klausner, Anthony S. Fauci, Lawrence Corey, Gary J. Nabel, Helene Gayle, Seth Berkley, Barton F. Haynes, David Baltimore, Chris Collins, R. Gordon Douglas, Jose Esparza, Donald P. Francis, N. K. Ganguly, Julie Louise Gerberding, Margaret I. Johnston, Michel D. Kazatchkine, Andrew J. McMichael, Malegapuru W. Makgoba, Giuseppe Pantaleo, Peter Piot, Yiming Shao, Edmund Tramont, Harold Varmus, Judith N. Wasserheit

Since the discovery of HIV 20 years ago and the demonstration that HIV is the cause of AIDS, the world has awaited the development of an effective preventive vaccine. Recent projections from the World Health Organization (WHO) and the Joint United Nations Programme on HIV/AIDS (UNAIDS) indicate that if the pandemic proceeds at its current rate, there will be 45 million new infections by 2010 and nearly 70 million deaths by 2020 (*1*). Although the scientific establishment has made extensive progress on extending survival of people with HIV and reducing maternal-fetal HIV transmission by antiretroviral therapy, transferring concepts for HIV-1 vaccines into clinical application has lagged.

Enhanced online at www.sciencemag.org/cgi/content/full/300/5628/2036

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Almost everyone involved in HIV vaccine development agrees that there is an urgent need to create and to evaluate systematically more candidate vaccines. Despite the wide variety of conceptual approaches to HIV vaccine design, the pace of development of new HIV vaccine candidates needs to be accelerated. In 2001 and 2002, only seven immunogens entered clinical trials. Only one candidate vaccine, aimed at eliciting neutralizing antibodies to a soluble HIV envelope protein, entered human phase III testing. Unfortunately, the recently released results from this trial did not demonstrate vaccine efficacy in the overall trial cohort (*2*). Although many approaches to producing immunogens have been discussed and initiated, systematic evaluation and optimization have proceeded slowly, in part because of factors such as the expense and complexities in advancing new candidate vaccines into phase I trials and scientific challenges.

These challenges include (i) the inability of current vaccine designs to elicit effective neutralizing antibodies against the circulating strains of HIV, (ii) the inability of current designs to prevent HIV from establishing persistent infection, (iii) the extensive global variability of HIV, (iv) the lack of understanding regarding the mechanisms of protection in the most effective HIV vaccine animal model system—the live attenuated approach, and (v) the lack of understanding of which HIV antigens induce protective immunity and which immune effector mechanisms are responsible for protection. The best engine for solving these major scientific challenges is the creativity of individual scientists working together in multidisciplinary problem-solving consortia, adequately resourced and linked to vaccine development capabilities. Two decades after the discovery of HIV, even with a variety of advanced cell and molecular technologies, the need remains for improved vaccine designs that will deal with the genetic and phenotypic variation of HIV-1 and effectively prevent the establishment of lifelong infection. The "enterprise" of HIV vaccine development must be designed as a high-quality collaborative research system that goes well beyond the high-quality but separate research projects that we have today.

We propose a model that could achieve the goals of a more efficient and integrated HIV vaccine research enterprise. We hope this Policy Forum helps open an international dialogue about options to achieve the goal of developing a safe and effective HIV vaccine in the shortest time possible.

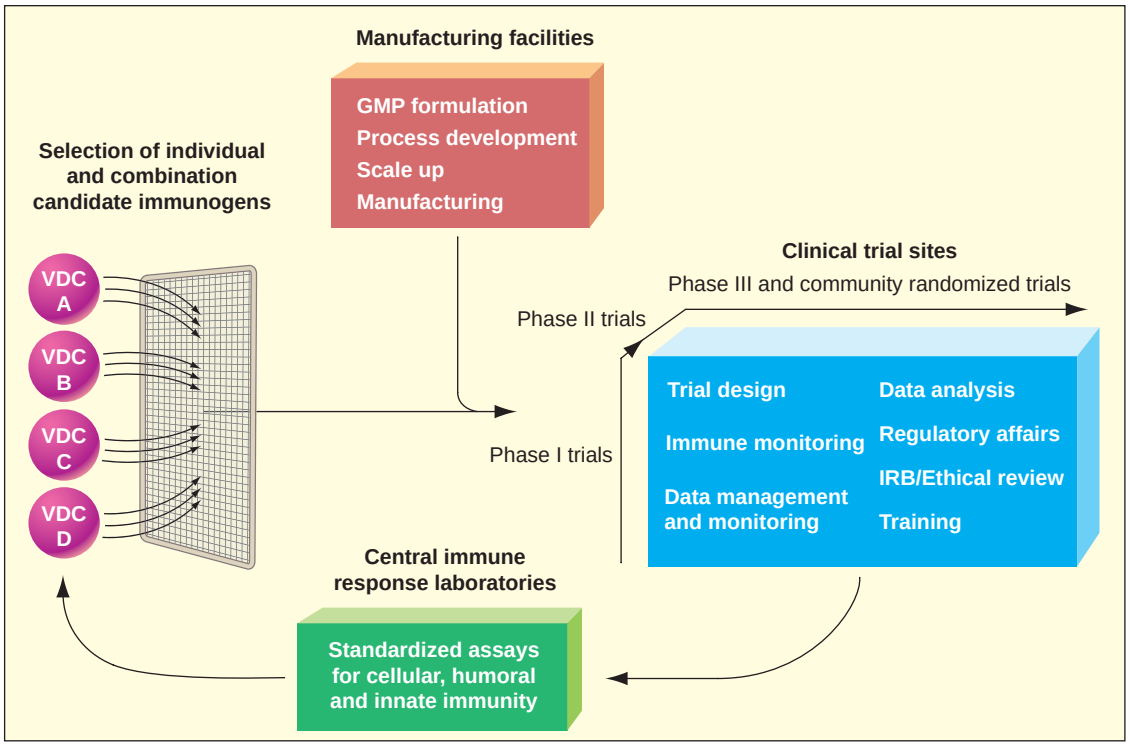
Basic Principles for the Enterprise

Vaccine development has historically been empiric and iterative, building on sequential successes to define correlates of immune protection that guide product development. Preclinical and clinical experiments and evaluation systems with objective measurements and analysis have been critical. Perhaps one of the most successful examples of such a concerted, empiric approach in medicine generally is the improvement in the treatment of childhood acute lymphocytic leukemia (ALL). Cure rates for children with ALL have improved from ~10% in the 1950s to more than 80% (and for some subtypes, 100%) in 2002. This increase has been produced almost entirely by a coordinated and iterative series of preclinical drug evaluations and subsequent clinical trials, in which partially effective drug regimens have been systematically altered (through studies of the effects of combination and sequence), to produce steady and significant improvement in survival as well as reduced toxicity.

HIV vaccine development has several similarities with developing treatment for ALL: (i) Although animal model data provide major conceptual insights, human clinical trials are ultimately required to define vaccine or drug effectiveness; (ii) the number of possible variables in reagent design and clinical outcome are large but definable; (iii) combinations of reagents

(vaccines for HIV, drugs for ALL) are likely needed to maximize benefit; (iv) no single regimen is likely, at least initially, to provide the optimal balance of efficacy, safety, and cost for all regions of the world; (v) a centralized, coordinated clinical trial and laboratory evaluation system facilitates progress in the field; and (vi) the program has substantial support from medical and political communities.

There are also features that are unique to developing an HIV vaccine. The pace of progression of the HIV epidemic, as well as the international, political, and economic toll, require a more rapid iterative process than the multidecade process described above. A well-coordinated global enterprise necessary to drive this scientific effort does not exist and must be created. The cost and process of developing new vaccine candidates, especially protein-based immunogens or noninfectious particles is typically substantially higher than those of new or modified drugs. Also, as the scientific risk of failure and the cost of vaccine development are high, reliance on industry to carry the major load for discovery and development for HIV vaccines is unrealistic. Thus, creative new public and public-private partnerships are necessary to drive the vaccine discovery effort, with industry's development expertise a key element that must be marshaled effectively.



Schematic of global enterprise for HIV vaccine development.

HIV Vaccine Development Centers

Even with the current paucity of prototype antigens in clinical trials, the portfolio of vaccine candidates contains significant overlap in approach [see "the pipeline project" (*3*) and (*4*)]. Increasing the diversity of approaches and coordinating the types of vaccines entering clinical trials are fundamental to speeding global HIV vaccine development. We believe that this requires the creation of a series of coordinated global HIV vaccine centers, each of which has the critical mass, focus, and scientific expertise, especially in vaccine development, to advance the rational development of a particular HIV vaccine approach rapidly and systematically. Features we believe vital to the success of such centers are as follows: (i) a critical mass of researchers with experience in basic and clinical research and an appreciation for the empiric aspects of vaccine development, (ii) concentrated dedication to the single goal of a global preventive vaccine, (iii) long-term commitment free of the strict requirements of the classical short-term measures of success used by academic institutions, (iv) sufficient resources to conduct costly preclinical development activities, and (v) collaborative arrangements with the private sector.

Each of these centers would have the funding, structure, and resources to devote itself to a specific vaccine development need and product. The sole focus would be to test systematically and to improve incrementally the immunogenicity and safety of the immunogens that they develop. The core of an integrated enterprise approach to HIV vaccine development would begin by conceiving of the world of potential vaccine concepts as a grid, with each cell representing a particular approach to immunogen construction, composition and delivery. We propose the development of as many HIV vaccine development centers (VDCs) as are needed to fully cover the agreed-on "cells" of the vaccine product pipeline grid; they would be supported by a variety of international funding agencies. The structure, scope, and scale of each VDC would be organized to explore fully design, development, and testing in preclinical and early-phase human trials of a particular approach with the capacity to examine an adequate range of variables of dose, delivery, adjuvants, and combinations. The goal would be to learn whether their approach is immunogenic, with what characteristics (nature of the immune response, breadth of response, intensity and persistence of the response) and whether any of the variables modify the response in a way that indicates whether and how to produce second- and third-generation candidates.

The structure of the VDCs could vary. These centers may be self-contained, as in the National Institutes of Health (NIH) Vaccine Research Center, or may be virtual centers such as those funded by the public-private partnerships of the International AIDS Vaccine Initiative (IAVI) and NIH. These VDCs may be developed within commercial or academic and/or research institutes, or through novel collaborations between different types of institutions, but would be unified by a central concept or theme. For example, multiple investigators and laboratories interested in the evaluation of a particular approach (e.g., specific viral vectors or protein antigens) would work together to systematically "cover the grid" of vaccine immunogenicity and toxicity for this specific vaccine vector or concept. Each center would be expected to work in collaboration with the larger global enterprise.

Areas of potential emphasis might be the development of novel adjuvants including recently discovered cytokines and chemokines, systematic modification of the envelope protein to maximize immunogenicity, bacterial vector design and delivery, optimized DNA and viral vector delivery, construction of immunogenic particles or structures, practical nonparenteral delivery systems and systematic approaches to define enhanced antigen presentation. Each center would systematically create reagents and conduct preclinical experiments that would provide vaccine prototypes for human clinical trials. We estimate that between 6 and 10 new VDCs are needed to comprehensively cover the approaches outlined in the figure (page 2037). As the most significant problem relates to developing vaccines that achieve rapid and broad viral neutralization, priority should be given to developing VDCs with this focus.

This system of collaborating vaccine developers would allow centers that work on cross-cutting technologies, such as novel adjuvant development or mucosal delivery, to work with the most promising antigens so that each component of a candidate vaccine would be optimized. This is currently lacking in HIV vaccine development. The purpose of this approach is to create a systematic and coordinated pipeline of vaccine constructs that can be tested, evaluated, and redesigned. It is especially important that combination vaccine regimens are developed and tested early and that there is a systematic evaluation of the strains and antigens used. Ways must be found to address how proprietary issues, such as exclusive licensing deals, can be reconciled with open communication and vaccine development paths that combine materials and technology platforms owned by different entities. Creative solutions to this problem will be required if the critically important role of industry in this enterprise is to be realized.

Organizations like NIH, IAVI, Agence Nationale de Recherches sur le Side (ANRS), and the European Union (EU) as well as pharmaceutical companies have funded vaccine development programs that are directed at many of these issues. Their work could form the foundation for this collaborative enterprise. Our concept could facilitate increased scale as well as greater communication and cooperation. This is particularly important among groups working on similar vaccine concepts. We expect that the infusion of funds, intellectual focus, and collaborations brought by such centers will result in increased participation of industry in HIV vaccine development. As product development and process engineering have largely resided in the biotechnology and/or pharmaceutical industry, incorporation of these skills should be an integral part of each VDC.

Vaccine Science Consortia

Many of the fundamental scientific questions impeding AIDS vaccine development have remained unchanged and unsolved since the identification of HIV as the etiologic agent responsible for AIDS. Answering these questions would provide crucial support to the VDCs and would be aided by the creation of a series of coordinated HIV vaccine scientific consortia. As with the vaccine research centers, we do not propose a specific structure for a given consortium, but the goal is to focus a range of researchers from many disciplines on a specific applied vaccine problem. The ultimate goal is to create effective, novel antigens for the pipeline. Commercial, academic, and research institutes must work together to solve the scientific challenge. Features we believe critical to the success of such consortia are (i) clearly defined goals and effective project management, (ii) dynamic scientific leadership and commitment of consortium members to the mission, (iii) a critical mass of researchers and the resources and infrastructure to rapidly translate preclinical leads toward clinical development, (iv) creative intellectual property agreements to provide incentives for data sharing and cooperative research, (v) long-term commitment free of the strict requirements of the classical short-term measures of success used by academic institutions, (vi) sufficient resources for each element of the consortium and flexibility to move resources between elements of the consortium, and (vii) collaborative arrangements with the private sector and/or the VDCs. Some of the possible scientific challenges are noted above, although these will undoubtedly change over time.

Development of Dedicated HIV-1 Vaccine Manufacturing Capacity

At present, there is inadequate capacity to produce vaccines to the standards needed for human clinical testing and insufficient resources devoted to the process of taking a research construct through the rigors of vaccine production. Therefore, the resources and facilities involved in manufacturing candidate HIV vaccines must be increased markedly. This entails the development of dedicated personnel and manufacturing facilities devoted to the process development, scale-up, formulation, stability, safety, toxicology, and production (in accord with "good manufacturing practice" or GMP) of experimental HIV vaccines, disciplines that are largely found in the private sector. A critical feature of this is the need for assay development to control the manufacturing process, something that is required for each technology and is often responsible for slowing product development. The importance of building manufacturing infrastructure has become even more acute as the major focus of HIV vaccine development has shifted from large pharmaceutical corporations to small biotechnology companies, or nonprofit or academic organizations, all of which have little or no vaccine manufacturing capabilities and experience. This lack of manufacturing capacity and expertise for vaccines and uniformity in production facilities has accounted for repeated delays in the HIV vaccine clinical trials programs. A system must be devised in which experienced industrial colleagues and facilities are devoted to the development and manufacturing of candidate HIV vaccines for human clinical trials. Expansion of this program must be coordinated with expansion of the product pipeline from the HIV VDCs.

Establishment of Standardized Preclinical and Clinical Laboratory Assessment

Although regulators and clinical trial specialists have recognized the need to standardize laboratory measurement in human clinical trials, preclinical assessments of candidate immunogens are still based largely on experiments in single research laboratories. As such, access to the primary data, standardization of the laboratory assays utilized, and interpretations of such data within the context of the field are generally not available. A more transparent and standardized preclinical evaluation system for candidate immunogens is essential for defining and developing successful vaccine regimens. For example, despite a wide variety of prototype vectors, only one standardized preclinical evaluation of their comparative immunogenicity has been initiated, and comparative human trials have not been performed. This issue has been recognized and begun to be addressed by NIH and IAVI, but should be considerably expanded.

Standardized protocols and immunogenicity measurements need to be broadly implemented at the preclinical and clinical stages of vaccine development to measure humoral and cell-mediated immunity and to provide a test bed for reproducibly assessing the immune response to HIV antigens and adjuvants. The preclinical discovery system provides a foundation on which choices for manufacturing and testing of formulations for human clinical trials can be made. Laboratories should be established to develop and deploy robust, repro-

ducible, and interpretable assays of immune response; to standardize reagents for such assays; and to incorporate quality-control measures for consistency. This paradigm might prove challenging to academic-based laboratories; therefore, linking these laboratories with clinical trials requires wider use of novel confidentiality agreements, working relationships, and information-sharing technologies. Such a preclinical laboratory program will also improve the pace of developing immunologic assessments in human clinical trials and will increase the likelihood of defining important correlates of immune protection.

Expansion of an Integrated, International Clinical Trials System

Large, comprehensive, coordinated, international clinical trials programs to conduct phase I, II, and III trials of candidate HIV vaccines have been established by the National Institute of Allergy and Infectious Diseases (NIAID), ANRS, IAVI, and the European Union. A rapid, iterative HIV vaccine trials enterprise will require expanded clinical trials capacity with emphasis on speed of accrual and retention of participants, high ethical standards, and enrollment of participating populations appropriate to the antigens being tested. Phase I/II clinical trials to define safety and immunogenicity are an integral part of vaccine development because, to date, animal models have been used with limited success in predicting human immune responses to HIV vaccines, especially to vector-based immunogens. The expanded global clinical trials system must therefore be considered part of vaccine product development and design. The clinical trials themselves must use standardized protocols and immunogenicity measurements. After an initial and rapid safety assessment in phase I trials, phase II trials must be adequately powered to define immunogenicity of new constructs as preclinical discovery and phase I/II clinical trials systems provide the foundation for choosing sets of large-scale phase IIb/III efficacy trials. Initial phase IIb/III clinical trials must assess laboratory and clinical efficacy and also attempt to define correlates of protection with validated assays.

Phase I safety and immunogenicity assessment of candidate HIV vaccine trials average 100 persons per protocol and phase II evaluations to define optimal dose and schedules, between 300 and 600 persons. The number of enrollees into phase III vaccine trials varies, depending on their goals, the nature of the population, and the transmission rate—but in general have averaged from 2500 to 10,000 persons per trial. To keep pace with the expanded pipeline, eventually the vaccine development enterprise would need to support a clinical trials program that enrolls about 5000 individuals in phase I/II and 30,000 persons into the phase III efficacy trials yearly. Multiple phase III trials will be needed to assess the protective efficacy of different vaccine concepts against different HIV-1 clades and in populations that may differ on the route of HIV-1 transmission or genetic background. In addition, gender, diversity in viral strains, duration, and magnitude of the ongoing epidemic are likely to influence vaccine efficacy. Most of these phase III trials will need to be conducted in developing countries, where most infections are occurring, and where a vaccine will have the most benefit. Assuring that true partnerships are developed with the research, medical, public health policy, and civic communities in those countries is essential and must begin early in the design of this enterprise. The international clinical trials system must engage local investigators, communities, ethical review committees, and regulatory bodies and must be coordinated with other national efforts to control the HIV/AIDS epidemic.

Optimizing Interactions Among Regulatory Authorities

Cooperation, communication, and sharing of information among regulatory authorities in various countries involved in licensing HIV vaccines are essential. We are not implying reduced standards in safety or manufacturing. In fact, the proposed system, with its more centralized manufacturing and immunogenicity programs, may be viewed as advantageous by regulatory bodies. This iterative process requires that regulatory bodies in a large number of regions or countries share access to preclinical and clinical information. Risk-benefit analyses for regulatory decisions should recognize regional variations in the social, economic, and health burdens of HIV and decisions by local regulatory authorities. Participation in the enterprise requires transparency and equality for all countries and regions involved. Vaccines that are partially effective should be made available for regions of the world that might benefit from their use at their explicit request while new trials and improved vaccines are being developed and evaluated.

Coordinating International HIV Vaccine Development

The Human Genome Project provides an interesting model for international coordination as many funders agreed on a scientific road map, voluntarily divided the work, and agreed to an evolving set of production standards. The frequent sharing of progress and problems allowed coordination, cooperation, and internal competition. The "governance" was driven by an open agreement of the scientists and the funders about the blueprint of the project, which allowed coordination without unnecessary duplication. No one entity actually ran the international genome project, although the leadership was assumed by the major funders and implementers. We believe that the time is right for the major scientific and product-development leaders and the stakeholders involved in the global HIV vaccine development enterprise to come together in an analogous way.

We propose the development of a road map for the Global Vaccine Enterprise that (i) would prioritize the scientific challenges to be addressed as well as product development efforts, (ii) would rapidly develop an implementation plan for all the components of the system, and (iii) would develop a plan that identifies the resources needed. The enterprise, however, should have multiple models for structures to accomplish these goals and must find solutions that engage the public and private sectors.

For this system to work, it must address several challenges. Funders and major stakeholders of HIV vaccine development must agree to a common vision so that they can coordinate their activities with other components of the enterprise. There must be considerable sharing of information among vaccine developers regarding preclinical investigation and trial results, with the ultimate goal of advancing to clinical trials. Solving problems of access to reagents, platforms, and technologies of potential commercial interest will be required. Finally, this must be a global effort. The research and development enterprise described here must build and include full participation of the developing world where this pandemic is raging. Tens of millions of lives are dependent on the development of a safe and effective HIV vaccine. It is essential that we aggressively explore all mechanisms that might expedite this process. While comparable vaccine access initiatives will also be required to ensure that HIV vaccines are made available to populations in need throughout the world, the expanded global AIDS vaccine effort proposed here hopefully would be a major step towards accelerating successful HIV vaccine development.

References and Notes

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The Global HIV/AIDS Vaccine Enterprise: Scientific Strategic Plan

Coordinating Committee of the Global HIV/AIDS Vaccine Enterprise

Introduction

In June 2003, an international group of scientists proposed the creation of a Global HIV Vaccine Enterprise [1]. The authors invited discussion of this proposal, and challenged scientists to identify new strategies and mechanisms to accelerate the global effort to develop a safe and effective HIV vaccine. This paper describes the processes that led to agreement on the major roadblocks in HIV vaccine development, summarizes current scientific priorities, and describes an initial strategic approach to address those priorities. Specific research is not prescribed. Rather, the intent is to stimulate both researchers and funders to explore new, more collaborative, cooperative, and transparent approaches to address the major obstacles in HIV vaccine development identified in the plan, in addition to continuing the productive, high-quality programs already underway.

The major difficulties encountered in the development of an HIV vaccine are scientific, not organizational.

The motivation behind the proposal for a Global HIV/AIDS Vaccine Enterprise was the recognition that development of an HIV vaccine remains one of the most difficult challenges confronting biomedical research today [2,3]. Fortunately, scientific progress has created new opportunities that could be harnessed more effectively through global coordination and collaboration. These new opportunities include an expanded HIV vaccine candidate pipeline, improvements in animal models, a growing database from clinical trials, and the availability of new quantitative laboratory tools that make comparisons among vaccine studies feasible. Confronting major roadblocks and harnessing these new opportunities requires an effort of a magnitude, intensity, and design without precedent in biomedical research, with the Human Genome Project as a potentially useful model [4]. More specifically, the critical scientific insights generated by the creativity of individual investigators, as well as small groups and individual networks, could be significantly augmented by a properly organized, managed, and systematized international effort targeted on the design and clinical evaluation of novel HIV immunogens. An international collaborative effort that addresses a shared scientific plan, provides information exchange among groups, links clinical trials with standardized laboratory assays and evaluation in animal models, applies new knowledge to improvements in vaccine design in an iterative manner, and supports a transparent process for decision making in all aspects of vaccine discovery, design, development, and clinical testing will prove critical to success.

The Global HIV/AIDS Vaccine Enterprise represents a novel paradigm to seek and identify international agreement on the critical roadblocks for developing an HIV vaccine and on creating a shared scientific plan that addresses those roadblocks (see Box 1). The Enterprise proposes to coordinate efforts at a global level, facilitate use of common tools and technologies, and help ensure access to optimized resources. Furthermore, the Enterprise approach is a way of behaving as a global community of problem-solvers, more openly sharing information, ensuring that the shared scientific plan is implemented, and basing decisions on evidence rather than advocacy.

It must be emphasized, however, that the major difficulties encountered in the development of an HIV vaccine are scientific, not organizational, and arise directly from the complexities of HIV and AIDS. "Small science" should not

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Abbreviations: BMGF, Bill & Melinda Gates Foundation; GLP, Good Laboratory Practices; IP, intellectual property; NIH, United States National Institutes of Health; R&D, research and development; SIV, simian immunodeficiency virus; UNAIDS, Joint United Nations Programme on HIV/AIDS; WHO, World Health Organization

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Box 1. Key Points in the Scientific Strategic Plan

- More new HIV infections and AIDS deaths occurred in 2004 than in any prior year (Figures 1–3). A vaccine is critical for the control of the pandemic.
- Development of an HIV vaccine is one of the world's most difficult and important biomedical challenges.
- Harnessing new scientific opportunities for HIV vaccine development will require an effort of a magnitude, intensity, and design without precedent in biomedical research.
- The Global HIV Vaccine Enterprise is an alliance of independent organizations committed to accelerating the development of a preventive HIV/AIDS vaccine based on a shared scientific plan.
- The scientific strategic plan was developed with the collaboration of over 140 scientists and other participants from 17 countries and several international organizations.
- The plan identifies critical unanswered scientific questions along the critical path for vaccine discovery, from antigen design to the conduct of clinical trials.
- Novel vaccine candidates need to be designed to induce high levels of broadly reactive and persistent immune responses against HIV strains circulating in different parts of the world.
- Standardization and validation of high-throughput laboratory assays conducted under GLP will allow comparison of results from different vaccines, which is a linchpin of rational decision making in vaccine development.
- The Enterprise will encourage decision makers to establish clear and transparent processes to identify and prioritize the most promising vaccine candidates.
- The Enterprise will seek to engage the best researchers who are willing to work in a highly collaborative manner and to dedicate the majority of their efforts to solve the fundamental roadblocks in HIV vaccine development.
- To mount an accelerated global search for a safe and effective HIV/AIDS vaccine, annual funding for such research should double—to US$1.2 billion per year.
- Several founding partners of the Enterprise have already committed, or are planning to commit, new funding to support the proposed Enterprise activities, and to create a culture of mutual accountability for the effective implementation of the scientific strategic plan.
- Enterprise activities are guided by an international Coordinating Committee, supported by different technical expert groups, including representatives from funders and implementers of HIV vaccine R&D.

be replaced with "big science." Both approaches must be undertaken. Creation of research environments that support the creativity both of individual investigators and of larger, collaborative efforts will accelerate the scientific breakthroughs needed to successfully develop a safe and effective HIV vaccine.

Scientific Priorities

Prioritization process. In August 2003, the authors of the Enterprise proposal invited a group of leading scientists, public health experts, and policy makers to meet at the Airlie House in Warrenton, Virginia, United States, to refine the vision for the Enterprise. The Airlie group agreed that the Global HIV/AIDS Vaccine Enterprise should be developed as an alliance of independent organizations committed to accelerating the development of a preventive vaccine for HIV/AIDS through implementation of a shared scientific strategic plan, mobilization of additional resources, and greater collaboration among HIV vaccine researchers worldwide [5].

The subsequent initial planning phase of the Enterprise involved leading government research agencies, private industry, non-governmental organizations, and funders involved in HIV vaccine research and development (R&D) activities, including the Bill & Melinda Gates Foundation (BMGF), the International AIDS Vaccine Initiative (IAVI), the National Agency for Research on AIDS of France (ANRS), the United States National Institutes of Health (NIH), the United Nations Joint Programme on HIV/AIDS (UNAIDS), the World Health Organization (WHO), and the Wellcome Trust. The Enterprise is expected to grow with time and include additional organizations and research groups willing to contribute to the implementation of its scientific strategic plan. A Steering Committee composed of representatives from several of the founding organizations provided guidance and coordination, with the BMGF serving as interim Secretariat.

Six Working Groups involving more than 120 participants from 15 countries, the WHO, and UNAIDS were formed to develop the scientific plan of the Enterprise. These Working Groups met from January to April 2004, identified critical unanswered questions, and proposed actions to address them. In May 2004, the Steering Committee of the Enterprise analyzed the recommendations from the Working Groups and identified the scientific priorities for initial action.

Several common themes emerged from the Working Groups. There was clear agreement on the key scientific challenges, as well as strong consensus that the HIV vaccine field has progressed to a point where it should be possible to answer some of the persistent questions more definitively. To meet these challenges, the Working Groups called for enhanced access to reagents and technologies, adequate resources, and strengthened human capacity in several key areas, especially in developing countries, where clinical trials need to be conducted. There was also agreement that the present way of doing business, which centers primarily on individually led research groups or networks, needs to be supplemented by establishing focused, collaborative structures and providing access to common standards and technologies, which would enable comparison of data and candidate vaccines. This would, in turn, support a rational process for decision making to advance candidate vaccines through the different phases of evaluation.

Vaccine discovery. One immediate goal is to design HIV candidate vaccines that consistently induce potent, broadly reactive, persistent neutralizing antibodies, as well as memory T cells that suppress viral replication and prevent escape of virus from immune control [6,7]. Additional research is also needed to identify how mucosal [8] and innate [9,10] immunity could be harnessed to develop effective HIV vaccines. The ability to develop effective vaccines would be greatly enhanced by an understanding of what specific immune response or responses correlate with vaccine-induced protection [11].

The current state of the art suggests a two-pronged strategy to accelerate the development of a safe and effective HIV vaccine. One component should center on candidate vaccines already in the pipeline, nearly all of which are designed primarily to induce T cell responses. In some animal models these T-cell-inducing candidate vaccines suppress post-infection viremia and

prevent or delay HIV disease, rather than prevent infection [12,13]. In studies of individuals infected with HIV, viral load correlates with efficiency of transmission [14], suggesting that a vaccine capable of suppressing viral load might reduce HIV transmission.

The second component should address critical gaps in scientific knowledge through carefully designed, focused, coordinated, and well-supported approaches. The fruits of this work will be a clearer understanding of what properties are needed for a successful vaccine and how to design candidates that incorporate those properties.

Scientific areas in which a more collaborative and organized Enterprise approach will be beneficial include the following: vaccine design based on the characteristics of recently transmitted viruses, evaluation of immune correlates of protection in animal models, and design of novel candidates vaccines that induce neutralizing antibodies and T cell immune responses.

Identifying which T cell candidate vaccine is most promising has become an urgent priority.

Vaccine design. Strategically, vaccines that are designed based on recently transmitted viruses hold the best hope of inducing relevant immune responses against currently circulating strains. Recent data suggest that the subset of viral strains that are sexually transmitted has unique genetic and antigenic properties, including greater susceptibility to neutralization than the bulk of circulating virus [15]. While such observations require confirmation, newly transmitted viruses are nonetheless the crucial targets of vaccine-induced immunity. Therefore, virological and immunological characterization of acute/early HIV infection should inform the design of vaccines and also guide the design of trials capable of determining whether immunization impacts virus levels and the course of HIV infection.

To address these issues, a representative number of virus strains derived from recently infected individuals representing those populations who will participate in vaccine efficacy trials, including populations in developing countries, should be obtained. These virus isolates should be subjected to a comprehensive genetic and biologic characterization, together with an analysis of host immune responses and the genetic background of those populations participating in the clinical trials.

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Figure 1. Adults and Children Estimated to Be Living With HIV as of the End of 2004 (Total: 39.4 [35.9–44.3] million)
(Map: UNAIDS/WHO)

This continuous and ongoing effort will require a multidisciplinary global approach, linking investigators who are conducting epidemiological and cohort studies (to allow for detection of acute/early infections), laboratory scientists working on the virology and immunology of acute/early infection and on the genetic characterization of affected human populations, vaccine designers and manufacturers, and clinical trialists. In addition, systems for data management and analysis that will facilitate the rapid translation of new information into improved vaccine designs need to be developed.

Immune correlates. Nonhuman primate models of AIDS offer opportunities to evaluate potential correlates of immune protection. While a particular immunization strategy that works in animal models may or may not predict protection in humans, important insights into potential immunologic mediators of protection would result from such studies. Several experimental vaccines induce varying degrees of protection against simian immunodeficiency virus (SIV) or chimeric simian/human immunodeficiency virus in rhesus macaques. In particular, studies using models in which a very high level of protection from acquisition of infection was achieved are needed, i.e., immunization with live attenuated SIV and attenuation of SIV infection by short-term antiretroviral treatment administered immediately after SIV inoculation [16,17].

To facilitate this process, assays for many different immune responses to SIV and chimeric simian/human immunodeficiency virus need to be standardized, validated, and made available to different research groups. Likewise, agreements need to be reached on those monkey challenge models that most closely resemble HIV transmission and infection in humans. Large numbers of animals will be needed to achieve statistical significance for experimental findings [18], which in turn will require expanded primate breeding and housing capability. A multidisciplinary approach that links virologists, immunologists, vaccine developers, primatologists, data and project managers, and others will be needed.

Neutralizing antibodies. There is increasing agreement that a successful vaccine needs to induce both humoral and cell-mediated immunity. Development of immunogens capable of inducing antibodies that neutralize primary HIV isolates from all genetic subtypes and regions of the world remains the most difficult challenge in the field of HIV vaccinology [19,20]. Success will likely require a deeper understanding of the structural motifs of the HIV envelope protein that interact with cellular receptors and/or

that are recognized by broadly neutralizing antibodies [19]. This strategy will require numerous well-characterized, broadly neutralizing monoclonal antibodies, the application of peptide and carbohydrate chemistry, structural biology, and genetic engineering approaches to immunogen design, and the use of iterative approaches guided by the immunogenicity of new designs.

Given the importance of these endeavors and the uncertainty as to what path will lead to success, multiple intersecting approaches need to be explored, including, for example, the design, production, and evaluation of (1) envelope proteins that stably reveal neutralization epitopes that may be only transiently exposed during viral entry into target cells, (2) immunogens that contain rigid, stable epitopes that mimic the portion or portions of envelope recognized by broadly neutralizing monoclonal antibodies, (3) modified envelope proteins that better expose existing relevant epitopes, and (4) molecules that resemble a stabilized version of the mature envelope trimer on the virion surface. These are examples of current approaches being explored, some or all of which may prove ineffective. Additional novel ideas need to be proposed and explored.

To achieve the above objectives, new tools and technologies such as those able to detect rare, broadly neutralizing monoclonal antibodies through large-scale screening of human sera will have to be developed. In addition, the very limited existing capacity to translate structural information into stable immunogen products needs to be expanded.

T cell vaccines. Nearly all current vaccine candidates in the clinical pipeline are T-cell-inducing vaccines, e.g., poxvirus recombinant vectors, adenoviral vectors, DNA constructs with or without adjuvants, and lipopeptides. The ongoing effort to evaluate these products and to develop new ones is considerable [21]. Identifying which T cell candidate vaccine or vaccines are most promising has become an urgent priority. However, these evaluations are being conducted within separate preclinical research groups and, to a lesser extent, separate clinical trial networks, with the result that candidate vaccines may not be optimally compared preclinically or clinically. This approach may result in delays in identifying the most promising candidates, and it risks devoting time and resources to inferior products, although it is recognized that the specific immune responses needed for a successful vaccine remain unknown.

The identification and optimization of promising candidates will require (1) defining clear, transparent processes for decision making, (2) establishing agreement on vaccine characteristics upon which decisions should be based, (3) developing and using validated assays to assess those parameters, to allow for preclinical and clinical comparison among candidates, and (4) establishing closer coordination and data-sharing among product developers, which will accelerate the availability of critical information needed to identify and further develop the most promising candidates.

Development of an HIV vaccine remains one of the most difficult challenges confronting biomedical research today.

Research is also needed to develop improved novel T-cell-inducing candidate vaccines, especially those that avoid or otherwise circumvent anti-vector immune responses [22], and those that induce persisting high levels of immunity, especially mucosal immunity. In addition, a thorough, systematic exploration of adjuvants that markedly enhance the quantity, quality, and durability of immune responses to HIV vaccines is needed.

Laboratory standardization. Comparison of results from preclinical and clinical studies is the linchpin of rational decision making regarding further development of vaccine candidates. Therefore, the initiation of approaches that will permit valid comparisons is crucial.

Progress to standardize and validate a limited number of T cell assays has been made within the laboratories of vaccine developers and within some partnering research networks. This approach now needs to be more broadly applied and extended to the analysis of neutralizing antibody responses. A robust infrastructure that develops, expands, and ensures broad access to quality assay technologies will allow valid comparison of data across trials and networks worldwide.

In order to achieve this goal, the following are required: (1) a decision-making process to select a set of robust assays, standardized and validated across laboratories, for measuring vaccine-induced immune responses in humans and animals; (2) wide availability of common reagents (such as peptides, control sera, and virus panels); (3) capacity for developing novel assays and reagents of potential value and for their translation to preclinical and clinical settings; (4) "core" laboratories that run selected assays and serve as a reference laboratory for satellite laboratories (clinical and preclinical work would take place in separate facilities, and clinical studies would require Good Laboratory Practices [GLP] conditions); (5) satellite laboratories located at or very near clinical trial sites to carry out a range of activities such as processing blood, storing and shipping specimens, and conducting basic immunological evaluation, and to participate in other Enterprise-organized activities such as acute/early infection studies; (6) an ongoing global quality assurance function encompassing all participating core and satellite laboratories and covering both routine safety as well as immunologic and virologic assessments; and (7) transfer of research assays and, when and where feasible, validated endpoint assays to satellite labs, including the necessary training activities.

In addition, new assay development has failed to keep pace with current understanding of the biology of the immune system and recent advances in technology. A more active program of applied research and assay development is needed to explore new concepts that would advance technical abilities and provide a better understanding of the immune responses generated by HIV vaccines.

Cellular immunity. Two assays are currently used for the primary evaluation and enumeration of antigen-specific T cells: Interferon-γ ELISPOT and multiparameter flow cytometry. The ELISPOT assay was initially developed to measure CD8+ T cell responses. Several observations in both mice and

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Figure 2. Estimated Number of Adults and Children Newly Infected with HIV during 2004 (Total: 4.9 [4.3–6.4] million)
(Map: UNAIDS/WHO)

humans have indicated that protective immune responses will likely require stimulation of both CD4+ and CD8+ T cell effector and memory functions; it is unlikely that induction of Interferon-γ-secreting T cells alone correlates with protective immunity [11]. Therefore, additional laboratory assays measuring multiple HIV-specific cell types as well as functional capabilities will be needed to thoroughly evaluate vaccine-induced immune responses. These assays should also permit rapid assessment of the magnitude and breadth of immune responses, and enumerate the specific epitopes that are recognized.

Humoral immunity. Different laboratories use different assays to measure antibodies that neutralize HIV and related viruses, SIV and chimeric simian/human immunodeficiency virus. These assays vary technically, but the most widely accepted assays measure reduction in virus infectivity in cells that express the receptors necessary for virus entry. Assays that offer the greatest value are those that are validated, amenable to high throughput, low in cost, readily transferable, and that can be performed according to GLP guidelines.

The ability to measure the magnitude and breadth of neutralization against diverse HIV strains is essential to evaluating responses generated by candidate HIV vaccines. Only with multiple strains of virus can neutralization breadth be ascertained in a meaningful way. Standard panels of HIV strains are in early stages of development. Expansion or extension of current standardization and validation activities, production and provision of necessary reagents, and access to quality assurance programs are needed to ensure worldwide comparability of assay results [23]. The strains of virus incorporated into a worldwide panel need to be carefully selected to reflect the current epidemic and should include early isolates from individuals at potential vaccine trial sites [24]. Molecular epidemiological studies and elucidation of the role of genetic factors and immune responses of the host in the transmission of HIV at the population level will also help guide vaccine design and evaluation [25,26]. Another specific priority is an assessment of the neutralizing antibody response generated in the recently completed Phase III trials of HIV envelope glycoprotein 120 candidate vaccines using a global virus panel. The results would establish a baseline level of neutralization potency and breadth that is non-protective, which would be extremely valuable in reaching informed decisions about advancing future antibody-based candidate vaccines.

As more HIV candidate vaccines enter the pipeline, current capacity will be exhausted.

A major obstacle to designing a suitable global virus panel is the paucity of information on neutralization serotypes. There is general agreement that if a reasonably small number of neutralization serotypes exist, their identification would guide the creation of an optimal panel of isolates for neutralizing antibody assays and the design of polyvalent immunogens. Although there is some controversy as to whether HIV-1 neutralization serotypes exist, the magnitude of benefit that would result if serotypes were identified warrants establishment of a neutralization serotype discovery program that employs the latest technologies.

Product development and manufacturing. Manufacture of vaccine candidates for large clinical trials and to meet eventual worldwide demand requires the development of processes for producing consistent, active vaccine batches on a large scale. Development of these bioprocesses must be integrated with analytical work (e.g., toxicity and stability testing), incorporate validated assays, and be applicable to the manufacture of sufficient vaccine to meet global needs after licensure. These processes are typically individually developed as a candidate vaccine advances from early clinical testing to late-stage evaluation and licensure. Worldwide expertise and capacity for this bioprocess development work is already limiting and exists almost exclusively in the private sector. As more HIV candidate vaccines enter the pipeline, current capacity will be rapidly exhausted.

The initial priority is to identify or establish one or more dedicated HIV vaccine bioprocess and analytical development groups that bring together the skill set and capacity to manufacture different promising candidates for clinical trials. The bioprocess development groups would also help train people and transfer manufacturing skills in whole or in part to manufacturing sites around the world. This training program would address the acute shortage of bioprocess experts.

At a later stage, building, acquiring, or contracting facilities to carry out bioprocess and analytical work and to produce several different types of candidate vaccines should be considered. Such facilities would further assist in transferring manufacturing technology to other production facilities, preferably in one or more developing countries. Decisions about which candidates a facility undertakes would be made through a well-defined, comprehensive evaluation process. The facili-

ties could eventually be expanded to provide production capacity to launch a vaccine for public health use, should no manufacturer be available to produce the vaccine quickly upon licensure.

Clinical trials capacity. As a growing number of HIV candidate vaccines begin to move through the clinical trials pipeline, the gap between existing global capacity and future requirements for conducting large efficacy trials has grown in magnitude and urgency, especially in developing countries. This gap in developing countries must be addressed through (1) increasing the quantity and quality of research staff, (2) establishing sustainable research facilities to support trials, and (3) expanding access to large, well-defined populations of uninfected people at high risk of HIV infection.

The recommended solutions take a long-term view and are aimed at building site capacity rather than preparing for specific trials. Sites should not be confined to conducting HIV vaccine trials but should be positioned

The acute shortage of qualified personnel is a major bottleneck to the conduct of clinical trials in developing countries.

to contribute to other research of public health importance to the community and the country, including, for example, other areas of HIV research (e.g., microbicides and treatment) and/or other diseases. Additional field trial sites must be developed to be able to conduct planned and anticipated efficacy trials. Sites should be selected in a strategic, data-driven manner, and should demonstrate the ability to recruit and retain large numbers of HIV-negative volunteers from populations with substantial HIV incidence. New efficacy trial sites should be developed in regions with emerging epidemics rather than only in areas with already-established disease. "Early-warning systems" must be available to identify these newly emerging sub-epidemics. Defining optimal methods for collection of HIV incidence data from populations at potential efficacy trial

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Figure 3. Estimated Adult and Child Deaths from AIDS during 2004 (Total: 3.1 [2.8–3.5] million) (Map: UNAIDS/WHO)

sites is essential. Whenever possible, efficacy trial sites should be linked to (1) academic medical centers to enhance research capacity and help train clinical researchers, (2) accredited local and regional laboratory facilities to provide infection endpoint and safety assessments, and (3) centers that can provide appropriate care and treatment to trial participants.

The acute shortage of qualified personnel is a major bottleneck to the conduct of clinical trials in developing countries with severe or rapidly emerging HIV epidemics. Development of intellectual capacity at these sites should emphasize (1) expanding research training opportunities for personnel in the broad range of topics required to conduct high-quality clinical research, (2) establishing and adequately supporting long-term career paths for such individuals, and (3) fostering political and social environments locally and nationally that support the conduct of clinical research. Building HIV scientific and operational expertise at clinical trial sites should be linked to other HIV/AIDS research activities (e.g., identifying and characterizing incident/early HIV infections, collecting newly transmitted strains, and measuring incidence in high-risk populations).

Site development must include strategies to develop or enhance existing capacity to deliver health care, including HIV prevention, care, and treatment, to the local community participating in clinical trials. Provision of, or referral to, basic clinical services such as voluntary counseling and testing and diagnosis and treatment of sexually transmitted infections will be essential.

In addition, site development should include building skills that are ancillary but critical to the actual conduct of clinical trials, such as educating communities, building community partnerships, managing site finances, and piloting applications through regulatory decision-making processes.

Regulatory considerations. The Enterprise must address a number of problems that currently impact the review of HIV vaccine trial protocols and that could delay future decisions regarding product licensure in developing countries. Most regulatory challenges arise from the fact that regulatory approvals are granted at the national level, but many developing countries lack the expertise, well-defined processes, clear delineation of authority, and/or other system components needed to make regulatory decisions expeditiously. As a result, new products are often licensed in these regions based on prior approval in the US or Europe and/or endorsement by the WHO. Under these circumstances, data specific to developing country populations (e.g., disease burden or childhood vaccination schedules) often do not enter into the decision making. The absence of defined pathways to approve products targeting a country's needs when a product is not also submitted to regulators in the US or Europe remains another obstacle. The Enterprise process has identified these action-item priorities: (1) harmonize and exchange information needed by regulatory bodies within the differing legal frameworks of different countries, (2) facilitate regulatory decision making, possibly using regional approaches for conducting reviews and making recommendations, (3) build regulatory

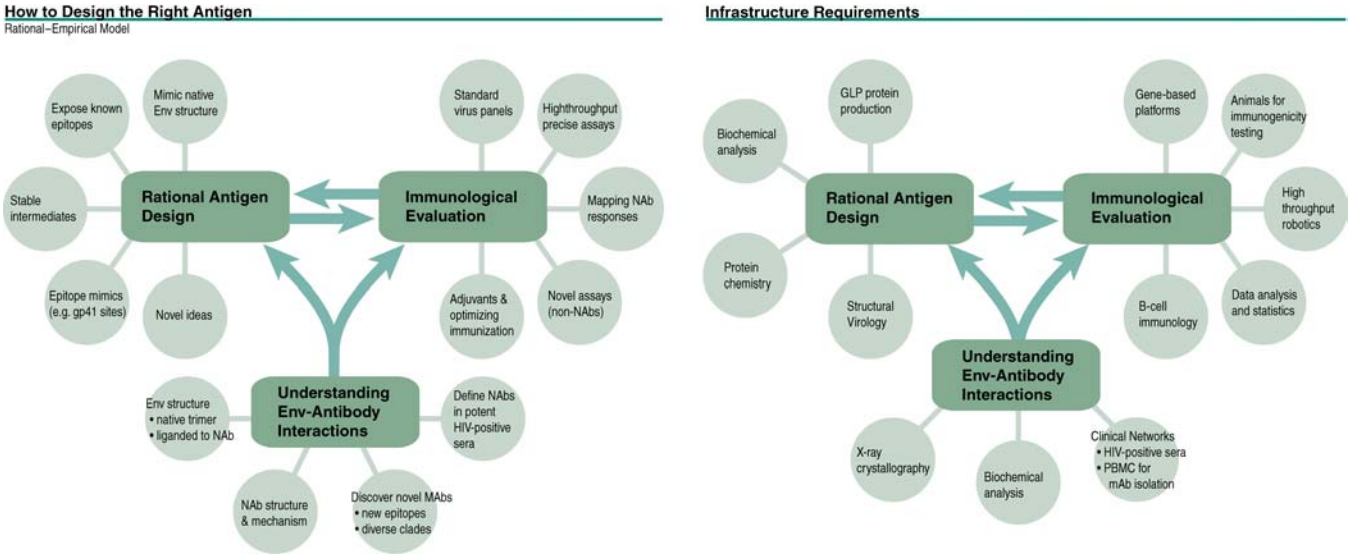

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Figure 4. A Possible Model to Address Key Scientific Questions through an Appropriate Organizational Infrastructure
(Courtesy of John Mascola; illustration: Giovanni Maki)

capacity, (4) perform risk/benefit evaluations in the context of differing epidemic dynamics and country needs and resources, (5) identify and remove potential scientific impediments to rapid regulatory decision making, and (6) address ethical issues that interface with regulatory decision making, such as ensuring informed consent and defining the degree to which trial participants should receive a standard of care that is higher than others in their community.

Intellectual property issues. Given the Enterprise focus on stronger collaboration, data sharing, and use of common materials and reagents, an intellectual property (IP) framework that facilitates this "enabling environment" is crucial for success. While IP issues may arise throughout the vaccine development process, at present the top priority is to stimulate early stage research and vaccine design by increasing scientific freedom to operate and sharing of data and biological materials.

Specific areas for further consideration include: (1) minimizing restrictions on freedom of operation, perhaps by early stage covenants not to litigate and followed by later stage agreements based on true valuations of IP; (2) sharing of information (including clinical trial data), materials, expertise, trade secrets, and platform technologies in a protected and secure manner while also remaining in compliance with national laws devised to prevent monopolies and insider trading; (3) recognizing the contribution of different countries to HIV vaccine development through approaches that assure affordable access to successful vaccines; and (4) maximizing access to essential technologies and inventions.

Scientific Plan

Scientific activities. On October 21, 2004, a group of participants from 16 countries, the European Commission, UNAIDS, and the WHO met to finalize the scientific plan and to discuss how to formulate specific actions.

Participants noted that the structure of an activity should depend on several factors, including, for example, the degree to which the activity can be predefined, the degree to which the creativity of academic researchers needs to be harnessed, and the mechanisms available to the funding organization.

A number of options were discussed, with consensus as to those that would fit various scientific priorities.

First, networks of focused consortia and real or virtual centers are well suited to systematically address many of the major scientific roadblocks identified in this plan. These consortia or centers would link to each other to ensure a comprehensive, systematic approach, sharing information so that each can be as productive as possible, and also to share reagents and procedures so that data among groups can be compared and, where possible, merged for analysis (Figure 4). The specific scientific areas that could be supported by consortia or centers include (1) addressing fundamental scientific problems, such as the definition of correlates of immune protection in selected animal models and the characterization of acute/early infection in potential vaccine trial sites; (2) designing and evaluating novel vaccines, such as immunogens that neutralize primary isolates, and improved T cell vaccines that avoid immunological escape and/or that induce persisting mucosal or persisting systemic responses; and (3) providing for a systematic evaluation of potential adjuvants. The success of consortia or virtual centers will depend on engaging the best researchers, getting them to work collaboratively and dedicate the majority of their effort to HIV vaccine research, resolving IP issues, obtaining support for researchers from their institutions, and keeping the group focused on specific, well-defined questions. More than one consortium may be needed for systematic coverage of vaccine design research (e.g., monoclonal-antibody-identified

epitopes, native envelope, and modified envelope).

Second, a global system of central laboratories linked to satellite laboratories that work together (using GLP) would provide a range of standardized functions, help ensure the quality of clinical research, and enable comparison of data from different trials (Figure 5). Together this system could (1) conduct preclinical or clinical assays, particularly critical endpoint assays that require standardization and/or validation; (2) develop, optimize, and validate new assays and platforms; (3) transfer assays from central labs to satellite labs; (4) develop and implement a global quality control/quality assurance program and proficiency testing for assays performed at central and satellite laboratories; (5) implement vaccine-related research that requires validated assays and close cooperation and collaboration among labs globally, such as a Virus Neutralization Serotype Discovery Program, and the characterization of recently transmitted HIV isolates; and (6) contribute to the development of technological infrastructure in developing countries.

Third, a number of contract laboratories capable of developing, acquiring, storing, and distributing common reagents will prove critical to the success of collaborative research and development projects, and to ensuring reagent quality. These reagents could include (1) peptides, antisera/antibodies, and viral isolates for immune assays, including a standard panel of virus strains and sera representative of the global genetic and immunologic variability of HIV, and (2) additional broadly neutralizing monoclonal antibodies, especially from non-clade B viruses, to facilitate elucidation of the motif or motifs they recognize. These contract laboratories would be expected to work very closely with and enable the work of Enterprise consortia, centers, immune assessment laboratories, and clinical sites.

Fourth, a network of Clinical Research Training Centers in developing countries could work collaboratively to ensure development of quality trial sites. These centers would (1) conduct or facilitate training of trial site personnel in activities that are generic to the conduct of clinical trials, as well as those specific for HIV vaccine trials, for example, an HIV vaccine fellowship program for developing country scientists; (2) coordinate and work together with other Enterprise consortia or centers, such as those established to characterize acute/early infection in developing country settings or to prepare a standard panel of HIV strains representative of currently circulating viruses; and (3) share standard operating procedures, vaccine development plans, and strategies for engaging and ensuring community and political support.

Fifth, a network of individuals and companies with manufacturing experience, particularly process development expertise, could link to consortia, centers, and others involved in vaccine development to provide development and manufacturing expertise to facilitate the advancement of improved HIV vaccine candidates.

The above structures are proposed to address the initial Enterprise scientific priorities. Additional consultative groups, reference and centralized facilities, and other mechanisms may be needed to facilitate collaborative work and strengthen the global capacity for the conduct of HIV vaccine research and development as the field progresses.

Different implementing and funding

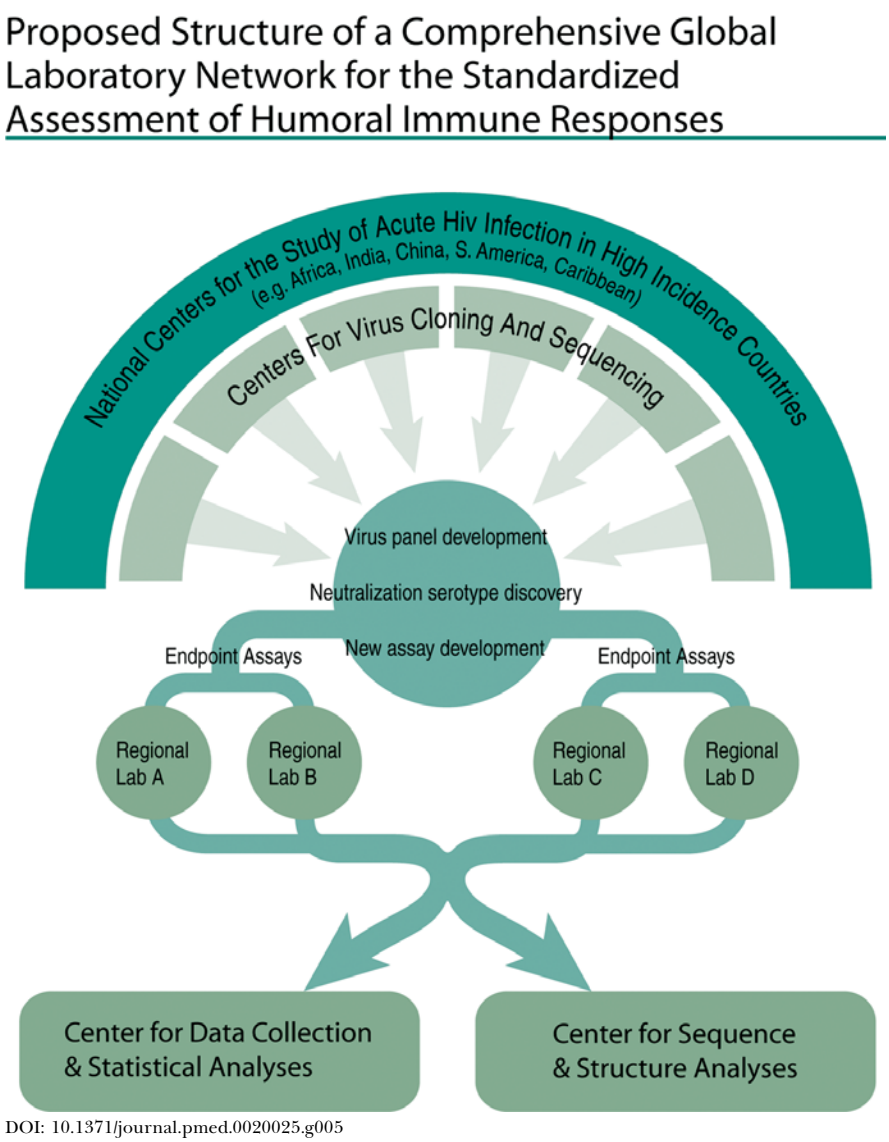

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Figure 5. A Possible Model for a Comprehensive Global Laboratory Network for the Standardized Assessment of Humoral Immune Responses

(Courtesy of David Montefiori; illustration: Giovanni Maki)

agencies will need to work in close collaboration to ensure harmonious implementation of the scientific plan. Initial actions should focus on the areas of vaccine discovery and standardization of laboratory assays, which are considered critical for the success of the Enterprise and the eventual development of a safe and effective HIV vaccine. Activities to address recommendations in the areas of product development and manufacturing, clinical trials capacity, regulatory considerations, and IP issues should be launched after these initial components of the plan are under way.

Regardless of timing, each scientific endeavor needs to outline specific strategies to ensure information exchange and capacity building among the collaborating partners and institutions. The funding mechanisms employed (i.e., contracts, grants, interagency agreements, etc.) will depend on the task to be accomplished and the needs and capabilities of each funding organization. In the spirit of coordination, collaboration, and transparency promoted by the Enterprise, two or more partners may jointly support one or more activities, taking care to avoid duplication in the use of their respective resources. When a research area is jointly funded, all communication regarding goals, research plans, progress, obstacles, etc., should be openly and transparently shared among all stakeholders—funders, project managers, and researchers.

Guiding principles. As an alliance of independent entities, the Global HIV/AIDS Vaccine Enterprise will be challenged to carry out three essential functions. One is to continue regular scientific assessments. The scientific priorities outlined in this paper will need to be monitored, re-evaluated, and updated. An evolving scientific plan must reflect lessons learned, new opportunities, and the influence of new scientific findings and new technologies. Revised versions of the scientific plan must be made fully and publicly available. The second essential function is to establish global processes. To optimize progress across a large and complex set of activities at the global level, standards, performance criteria, and processes for data sharing, communication, and convening must be established. The Enterprise will convene fora to address policy issues such IP, clinical trials, site development, and regulatory hurdles. And the third essential function is shared accountability. The partners in this alliance will need to create a culture of mutual accountability for the effective implementation of the scientific strategic plan. Since the Enterprise is not a single organization, a shared "way of doing business" is one of its most important defining traits. Articulating an explicit set of "working principles" is therefore crucial to the identity and smooth functioning of the Enterprise.

For the Enterprise as a whole the following conditions apply: (1) the central task is to develop and implement an ambitious scientific plan with the necessary scale, balance and sequence of activities, and structure to carry it out; (2) the plan must focus on critical roadblocks that would benefit substantially from global collaboration while fostering continued R&D by individuals, small groups, and individual networks; (3) the incentives holding the alliance together will include collaborative arrangements and structures that give people the resources, necessary critical mass, centralized facilities, common reagents, assays and technologies, and data they need to effectively remove critical roadblocks; (4) all activities will reflect the commitment to create an environment that maximizes the ability of participants to share data and biological materials, e.g., through the use of common standards for measurements and appropriate IP arrangements; and (5) the Enterprise also commits to working for rapid global access to a successful vaccine.

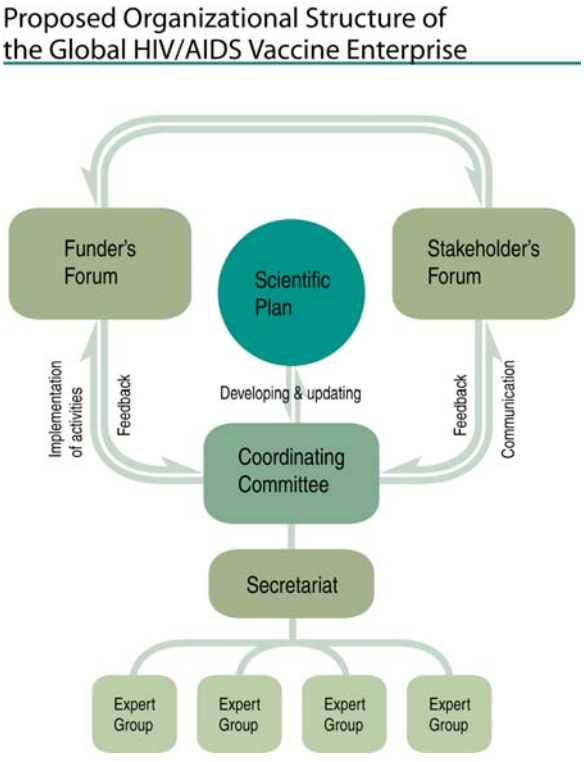

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Figure 6. Proposed Organizational Structure of the Global HIV/AIDS Vaccine Enterprise (Illustration: Giovanni Maki)

For participating investigators and organizations, key principles include (1) the willingness and desire to work in an open, collaborative fashion, sharing data and reagents in a collegial fashion, with the appropriate balance between productive competition and effective collaboration, and (2) the willingness and ability to devote the majority of their time to tackling these problems within a focused environment, completely committing to solve the problems at hand.

Organizational structure of the Enterprise. The implementation of the scientific plan of the Enterprise will be overseen and supported by the organizational structure described in Figure 6.

The Coordinating Committee will facilitate all aspects of the Enterprise's activities. This committee consists of representatives of the Enterprise founders as well as additional scientific leaders selected from inside and outside the field of HIV vaccine research and development. The committee will develop procedures for term rotation and inclusion of new members, to ensure appropriate representation of all relevant partners, and will engage external stakeholders for advice, expertise, and assistance, appointing technical expert groups as needed. A Secretariat will provide logistical and

administrative support to the Coordinating Committee and Enterprise partners. The BMGF will serve as Interim Secretariat until a permanent Secretariat is established.

The Funders Forum will be an open forum of sovereign, independent funding organizations, starting with a nucleus of those who already embrace the principles of the Enterprise and who are actively supporting or intend to support and fund HIV vaccine research and development. Members of the Funders Forum will be high-level decision makers within the ranks of funding organizations and governments, as close as possible to the source of resources. Since the Enterprise is not a discrete organization with a pool of money, funders will support specific areas using their own mechanisms, according to their own practices and policies, and following Enterprise principles. The scientific plan will provide guidance that may help funders better align existing resources but, more importantly, will facilitate the efficient and focused application of new resources as they become available. Multiple funders who wish to support a single Enterprise-defined project could form collaborative agreements, memoranda of understanding, or other forms of written agreement among themselves to outline their respective roles and responsibilities; address IP, program management, oversight, and other issues; and establish mechanisms for communication and conflict resolution. The funders with greatest flexibility could provide incentives for sharing reagents and data, and linking projects together, e.g., by supporting the additional work that nationally or regionally funded laboratories would need to undertake in order to participate in a global network, or by supporting a program to develop and share reagents.

The road to success will be a bumpy one.

In some cases, funders may wish to support an implementing organization that will take responsibility for managing the project and reporting back to the funder and other stakeholders. In other cases, funders may have the capability and capacity to play a substantial role in facilitating the project. In still other cases, funders may have the capability to assume a leadership role in overseeing the conduct of the activity, particularly in cases where the activity is well defined in advance.

In addition, an Annual Stakeholders Forum will be organized to bring together the broader community of scientists, policy makers, public health officials, and community representatives involved in the search for an HIV/AIDS vaccine. This meeting will serve as a forum to (1) update the broader community on Enterprise activities and progress, and (2) provide the community with a mechanism for feedback and dialog.

Funding issues. Global expenditures on HIV vaccine research and development in 2002 were tentatively estimated to be on the order of US$624–670 million, the large majority (67.3%) provided by the public sector, followed by the philanthropic sector (17.4%) and industry (15.3%). An analysis of how those funds have been invested revealed that the large majority (43.1%) is being used in preclinical research activities, followed by clinical trials (28.2%), basic research (20.7%), cohort development and clinical trial infrastructure (6.5%), and vaccine education, advocacy, and policy development (1.4%) [27].

The largest funder of HIV vaccine research and development activities has been the NIH, with almost US$350 million in 2002. The NIH budget for HIV vaccine research has grown from less than US$50 million in 1996, to an estimated US$514.6 million for 2005, corresponding to 17.6% of the NIH total HIV-related research budget for 2005.

The Enterprise Coordinating Committee will analyze the additional financial requirements to fully implement the scientific plan of the Enterprise, and the Enterprise Secretariat will explore options to leverage these funds from the public and private sector. Initial estimates by Enterprise partners suggest that US$1.2 billion per year, or double the current expenditures on HIV vaccine research and development, will be needed. Although this amount may appear unrealistic at present, it would represent only a fraction of the total global expenditures in response to the AIDS pandemic and a very reasonable investment in view of the enormous social, political, and economic consequences of the pandemic. However, it is essential that the proposed increase in funding for HIV vaccine R&D be additional to existing AIDS expenditures, and not at the expense of current prevention, treatment, and care efforts.

The founding partners of the Enterprise, including the NIH, the BMGF, and the Wellcome Trust have already committed, or are considering committing, resources towards new initiatives that will begin to enact portions of the Enterprise scientific plan over the next six to nine months. Each funder will utilize their own funding processes and will align the design, scope, and scale of programs to those laid out in this plan. For example, the NIH National Institute of Allergy and Infectious Diseases will establish the Center for HIV Vaccine Immunology, which will target several scientific priorities identified here.

Political support. As a sign of global recognition of the importance of better, more strategic coordination in the search for an HIV vaccine, the "Group of Eight" leading industrialized nations in June 2004 endorsed the goals of the Enterprise and agreed to review progress in implementation at its 2005 summit meeting in the United Kingdom [28]. Likewise, on October 19, 2004, Ministers of Health from seven European countries (France, Germany, Italy, the Netherlands, Spain, Sweden, and the United Kingdom) adopted a statement of intent to coordinate efforts to accelerate research for an HIV vaccine within the context of the global effort.

Next Steps

With almost 5 million new HIV infections and 3 million AIDS deaths occurring every year worldwide, the development of a safe, effective, and accessible HIV vaccine represents one of the most urgent global public health needs. This global emergency led to the proposal to harness the power of science to find a definitive solution to one of the most catastrophic health problems of our time. The Global HIV/AIDS Vaccine Enterprise has evolved over the past 18 months from a concept proposed in a scientific journal by a cadre of researchers to a global consensus concerning the major scientific roadblocks facing HIV vaccine devel-

opment, a strategic approach to address those roadblocks, and guiding principles for the plan's implementation in a manner and degree commensurate with the challenges at hand. Several organizations have already embraced the Enterprise concept and are moving to tackle portions of the scientific plan. Still, much more remains to be done. The road to success will be a bumpy one requiring the energy, commitment, and action of a wide number of government and non-governmental organizations globally. Recognizing the enormity of the roadblocks as well as the potential benefits of a safe and effective HIV vaccine, it is essential that many more organizations and agencies contribute additional expertise and resources and work together as a global community in a cooperative, collaborative, and transparent manner to fully implement the Enterprise scientific plan. ■

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